

Prospective Randomized Clinical Trial of Accelerated Re-Epithelialization of Split-Thickness Skin Graft Donor Sites Using Injectable Platelet-Rich Fibrin (I-PRF)

Premasak Sakarinpanichakul, MD¹

Watchara Burapholkul, MD¹

Pucharaporn Jiengjariyanont, MD²

¹Division of Plastic and Reconstructive Surgery, Department of Surgery, Buriram Hospital, Buri Ram, Thailand

²Department of Anatomical Pathology, Buriram Hospital, Buri Ram, Thailand

Abstract

Background: Autologous platelet-rich fibrin (PRF) is a fraction of blood with a high concentration of platelets and multiple growth factors. Its application has shown promising results in wound care. However, it remains controversial whether applying PRF to donor site wounds of split-thickness skin grafts (STSGs) improves the epithelialization rate. This study aimed to determine the effect of injectable platelet-rich fibrin (I-PRF) on the epithelialization of donor-site wounds in STSG.

Materials and Methods: This randomized controlled clinical trial included 30 patients who underwent STSG procedures at Buriram Hospital between November 2023 and February 2025. The donor site wounds were divided into two groups for the study. The intervention group received an I-PRF and paraffin gauze, while the control group received paraffin gauze alone. The evaluation assessed the time required to re-epithelialize donor-site wounds and measured epithelial thickness after full re-epithelialization.

Results: The mean age of the patients was 50.7 ± 18.7 years, and 63.3% were male. Time to complete epithelialization of donor wounds did not differ significantly between I-PRF and control groups (11.9 ± 2.6 days vs 11.9 ± 2.7 days; $p = 0.851$). The mean epithelial thickness of the I-PRF group was higher than that of the control group, but the difference was not statistically significant (208 ± 110 mm vs 197 ± 118 mm; $p = 0.698$).

Conclusion: Compared to traditional therapy, a single application of injectable platelet-rich fibrin did not significantly influence the re-epithelialization of an STSG donor wound.

Keywords: Platelet-rich fibrin, Injectable platelet-rich fibrin, Epithelialization, Donor site

INTRODUCTION

Split-thickness skin grafts (STSGs) consist of varying dermal layers and are a commonly used reconstructive technique for closing defects that cannot be closed primarily. The donor site of the STSG generally heals (re-epithelializes) in 7-21 days.¹ Theoretically, an ideal donor site wound dressing should be easy to apply, promote rapid re-epithelialization without adhering to the wound bed, reduce inflammation, minimize disease transmission and host immune response, significantly decrease wound pain, and be cost-effective.^{2,3} Numerous

studies are using various materials or methods to improve the re-epithelialization of the donor site after STSG, such as modern dressings,^{4,5} biological dressings,⁶⁻⁹ drugs¹⁰ and medical equipment.¹¹

A platelet-rich product is a biological preparation containing a platelet concentration higher than the baseline of whole blood. Growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor β (TGF- β), epidermal growth factor (EGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF), are released

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Corresponding author: Premasak Sakarinpanichakul, MD, Division of Plastic and Reconstructive Surgery, Department of Surgery, Buriram Hospital, Buri Ram, Thailand; E-mail: tommy.premasak@gmail.com; Phone number: +6686 873 8737
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after platelet activation to enhance wound healing.^{12,13} Platelet-rich products are classified into two main categories: platelet-rich plasma (PRP) and platelet-rich fibrin (PRF).¹⁴ Numerous studies have utilized platelet-rich products to enhance the healing of both acute and chronic wounds.^{15,16}

PRF is a second-generation platelet concentrate developed by Choukroun et al. in 2001 that does not use anticoagulation factors. There are two types of PRF: a solid form and a liquid form. The solid form is the original PRF formulation developed by Choukroun and colleagues. The injectable liquid form of PRF (I-PRF) was developed by reducing the centrifugation force to 700 rpm (revolutions per minute) and 60g RCF (Relative Centrifugal Force) for 3 minutes.¹⁷ I-PRF has been used in various oral and maxillofacial procedures,^{18,19} as well as in wound healing.^{20,21} However, few studies have directly examined the relationship between I-PRF and the healing of donor-site wounds following STSG.²²⁻²⁴

This study aimed to assess the potential benefits of I-PRF on wound healing in donor-site STSG wounds compared to the established standard treatment at our hospital.

MATERIALS AND METHODS

Study Design

This study was a prospective, randomized, controlled trial comparing the effectiveness of a paraffin gauze dressing plus I-PRF with that of the paraffin gauze dressing alone. The study was approved by the Ethics Committee of Buriram Hospital (Protocol No. BR 0033.102.1/73) and registered with the Thai Clinical Trials Registry (TCTR). The TCTR identification number is TCTR20240704001.

Material (Dressings)

A standard dressing for STSG donor site in our institution is paraffin gauze containing 0.5% chlorhexidine acetate (Bactigras; Smith & Nephew Medical Ltd.). This antiseptic, low-adherent dressing soothes and protects the wound while helping reduce infection and inflammation. The paraffin gauze allows the free passage of viscous exudate through the grid into a secondary dressing while maintaining a moist wound bed.²⁵ We assigned the paraffin gauze (Bactigras) to the control group.

We prepared the I-PRF according to the low-speed centrifugation concept¹⁷ and assigned the Bactigras plus I-PRF to the intervention group.

Preparation of I-PRF (Figure 1)

- After harvesting the STSG from the donor site, 20 ml of peripheral venous blood was collected into a sterile 10 ml plastic syringe without a plunger (Nipro). The syringe tip was covered with a cap, and the barrel was held with a sterile surgical drape. No anticoagulants were used during the procedure.
- Centrifugation was performed immediately at 700 rpm (revolutions per minute) for 3 minutes at room temperature (MRC Laboratory Equipment, Model: SCEN-206).
- After centrifugation, a yellow I-PRF formed at the top layer, while other components settled at the bottom.
- The yellow fluid at an upper level was extracted using a 16G needle, 2 inches.

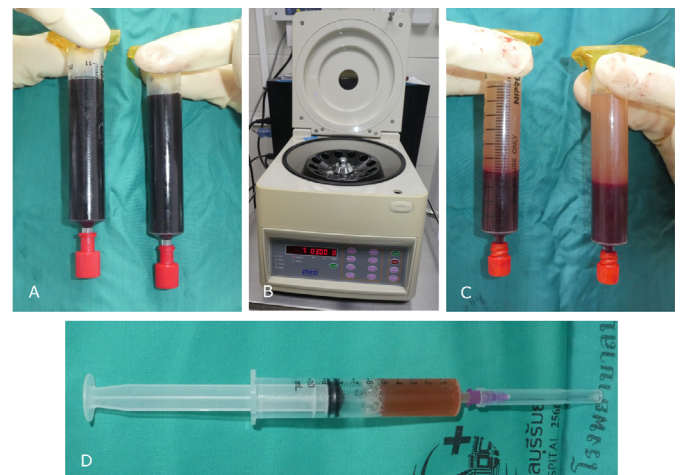


Figure 1 A) Collection of 20 ml (10 ml each × 2 tubes) of whole blood in sterile plastic syringes without a plunger, with the tip cap covering the syringe tip, and the barrel held with a sterile surgical plastic drape. B) A centrifuge was used to prepare I-PRF from blood samples. C) Appearance of I-PRF after centrifugation. D) I-PRF collection after extracting from the tubes.

Sample size

The required sample size was calculated using the formula for the difference between two correlated quantitative measurements (paired means):

$$n/group = \frac{2 \left(\frac{Z_{\alpha} + Z_{\beta}}{2} \right)^2 \sigma^2 (1 - \rho)}{(\mu_1 - \mu_2)^2}$$

where $\alpha = 0.05$ ($Z_{\alpha/2} = 1.96$), $\beta = 0.10$ ($Z_{\beta} = 1.28$, power = 90%), and ρ is the correlation coefficient, estimat-

ed at 0.5 as a conservative value. The pooled variance(σ^2) and mean values (μ_1 , μ_2) were derived from a previous study by Senada et al.²² which reported a mean epithelialization time of 11.55 ± 1.39 days in the experimental group and 13.45 ± 1.70 days in the control group. Substitution into the formula indicated a minimum requirement of 8 participants. After adjustment for an anticipated 30% attrition rate, the final required sample size was 12 participants. In practice, 30 participants per group were enrolled to increase statistical power, improve the precision of effect estimates, and better capture clinical variability.

Patients and randomization

Thirty patients with skin defects requiring partial-thickness skin grafting were enrolled in this study. The primary indications for STSG were reconstruction of defects following cancer excision (10 cases), trauma-related wounds (9 cases), burn injuries (6 cases), and post-debridement wounds from infection (5 cases). All patients provided written informed consent and were permitted to use their photos before enrollment. The donor sites were equally divided and randomized using one of two sealed envelope techniques for the intervention group. Both proximal and distal sides were labeled. Other officers allocated the wound dressing on the day of surgery before the procedure.

Outcome variables

The primary outcome was the time to complete donor-site healing (>90% re-epithelialization).²⁶ The secondary outcome was the epithelial thickness of the donor site after complete re-epithelialization.

Inclusion and exclusion criteria

The study included patients aged 18 and older who were hospitalized at Buriram Hospital and underwent STSG between November 2023 and February 2025.

The exclusion criteria were:

- Refusal to participate
- Patients with hematologic disorder
- Patients with a platelet count of less than 100,000 platelets per microliter or a history of platelet dysfunction
- Patients with severe cardiovascular, connective tissue disease, end-stage renal disease, liver cirrhosis or liver failure, cancer, septicemia, or other diseases that may affect wound healing
- Patients with severe malnutrition
- Pregnancy

- Patients with systemic steroids used within 2 weeks before surgery
- Patients with an immunocompromised host
- Patients with HIV infection
- Inflammation or infection of the donor site

Technique

The first author, a plastic surgeon (P.S), performed all operations under general anesthesia. The STSGs were taken from the thigh with the Air Zimmer Dermatome skin grafting system (Zimmer, Inc., Warsaw, US) at a depth of 0.175 mm. The donor site was divided into three zones: proximal, middle, and distal. The proximal and distal zones were split in half and randomly assigned to either the control or intervention group. To minimize contamination or bias, the middle zone was approximately 2 cm wide at the midline; it was defined as the border between the proximal and distal zones and was excluded from the evaluation (**Figure 2**). After harvesting STSG, the surgeon measured the wound length and width with a sterile ruler and photographed the donor site. The I-PRF was prepared, and the designated dressings were applied to the control and intervention groups (**Figure 3**). The assigned wound-dressing materials were then covered with sterile dry gauze and secured with an elastic bandage. To minimize the risk of cross-contamination during bandage application, each donor site zone was covered with individual sterile gauze before being secured with an elastic bandage, ensuring no fluid communication between the intervention and control sites.

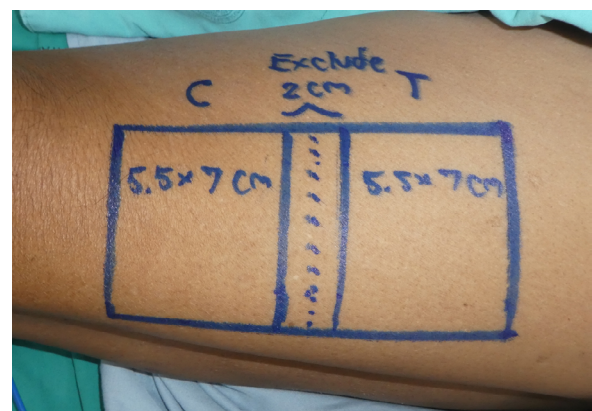


Figure 2 The area was divided into three zones (proximal, middle, and distal zones). The proximal and distal zones were randomly assigned to either the control or the intervention group. The middle zone was 2 cm wide at the midline. It was defined as the border between the proximal and distal zones and was not included in the evaluation.

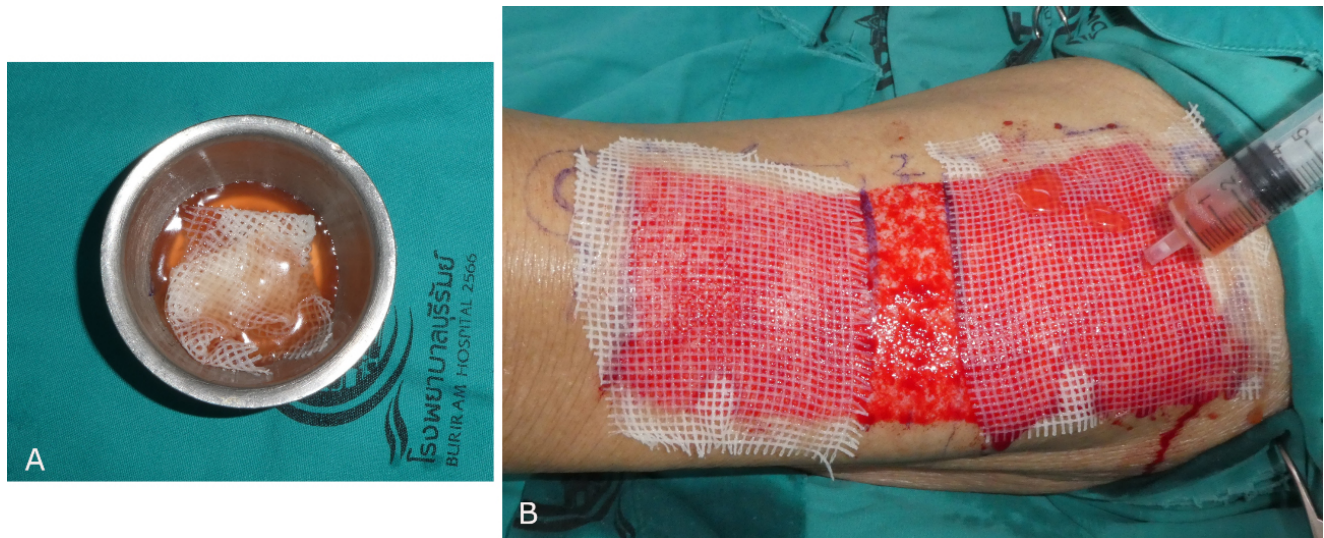


Figure 3 A) A paraffin gauze soaked in I-PRF preparation for the intervention side. B) A paraffin gauze dressing for the control side and a paraffin gauze soaked in I-PRF + I-PRF instillation for the intervention side are applied.

Postoperative management and follow-up

We evaluated wound-healing time, donor-site complications (signs of inflammation or infection), and microscopic epithelial thickness.

Wound healing was assessed visually by two independent plastic surgeons, experts in wound care, by measuring the re-epithelialization rate across the wound surface area. The initial dressing was changed on postoperative day 7. Subsequent dressings were altered based on the rate of re-epithelialization as follows: every 3 days if the rate was less than 50%, every 2 days if it was between 50% and 75%, and daily if it exceeded 75%. This process continued until the wound was fully healed. Photographs were taken during each dressing change. Complete healing of the donor site was defined as more than 90% re-epithelialization of the wound.²⁶

After complete epithelialization, a 4-mm punch biopsy was performed on both the control and intervention sides using a KAI biopsy punch (KAI Industries Co., Ltd.), and the specimens were fixed in 10% natural formaldehyde for microscopic measurement of epithelial thickness. Paraffin-fixed specimens were stained with hematoxylin and eosin (H&E). The average epithelial thickness from 25 randomly selected microscopic fields from each H&E-stained specimen was then recorded by two independent, blinded pathologists. (Figure 4).²⁷

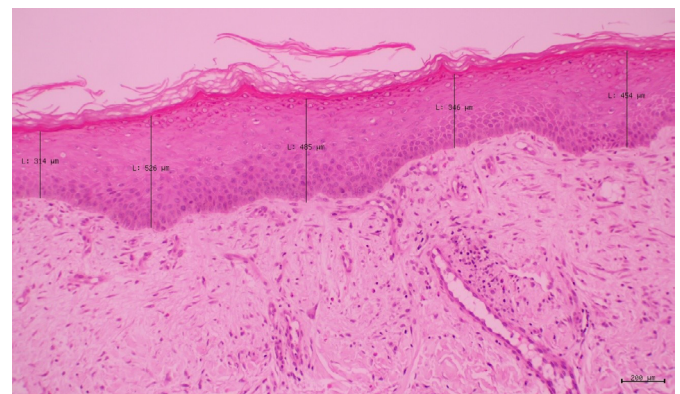


Figure 4. Specimen from the donor site after hematoxylin and eosin (H&E) staining. The section displays the epithelial thickness measurements from 25 randomly selected microscopic fields (see an example of 5 points in the image). × 10

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. Inter-rater reliability for both the epithelialization rate and epithelial thickness was assessed using the Intraclass Correlation Coefficient (ICC). For the primary analysis, paired t-tests were performed to compare the mean epithelialization rate and epithelial thickness between the two groups. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Inter-rater reliability

Inter-rater reliability for both the epithelialization rate and epithelial thickness measurements was assessed using a two-way random-effects model with absolute agreement. The average measure, Intraclass Correlation Coefficient (ICC), for the epithelialization rate was 0.9 (95% CI: [0.7-1.0]), indicating excellent reliability. Similarly, the epithelial thickness measurement showed good reliability with an ICC of 0.9 (95% CI: [0.6-1.0]). Due to the high level of agreement between the two independent raters for both assessments, the average of their scores was used for all subsequent data analyses.

Epithelialization assessment

Thirty patients were included in the study, and all completed the follow-up period. **Table 1** shows the baseline data of the enrolled patients. The mean age of the participants was 50.7 ± 18.7 years.

Table 1 Demographic data of the patients

Characteristics	Mean $\pm$ SD or N (%)
No. of patients	30
Age, years	
Mean	50.7 ± 18.7
Range	18-84
Sex	
Male	19 (63.3%)
Female	11 (36.7%)
Site of STSG	
Right thigh	10 (33.3%)
Left thigh	20 (66.7%)

The mean area of donor-site wounds for evaluation was 49.4 cm² (range: 20-96 cm²) in both the control and I-PRF groups. The mean wound-healing time of donor-site wounds showed no statistically significant difference between the control and I-PRF groups ($p = 0.851$; **Table 2**).

Figure 5 compares the postoperative clinical outcomes of the I-PRF and control sides with respect to re-epithelialization of the donor area.

Table 2 Time to complete epithelialization

Groups	Mean $\pm$ SD (days)	95% CI for Mean Difference	<i>p</i> value*
Control (Bactigras)	11.9 ± 2.7		
Intervention (Bactigras + I-PRF)	11.9 ± 2.6		
Difference	0.0 ± 1.0	[-0.3, 0.4]	0.851

*Statistical analysis was performed using a paired t-test.

Case (1)



Case (2)

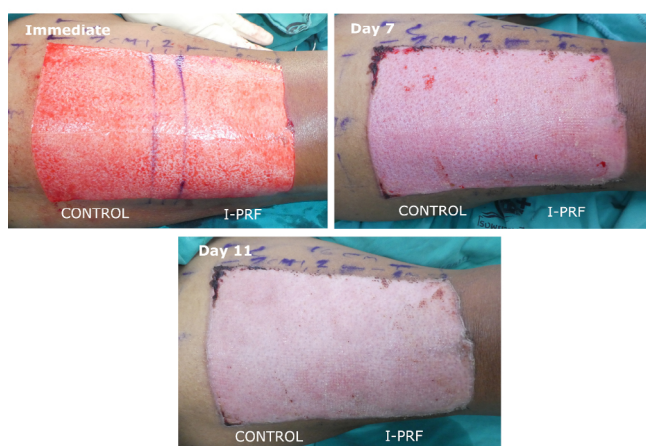


Figure 5 Postoperative results for two patients regarding re-epithelialization are presented. Case (1) includes images of the immediate donor-site wound, along with postoperative results on days 7, 10, and 14. Case (2) shows the immediate donor site wound and the postoperative results on days 7 and 11.

Epithelial thickness measurement

After complete epithelialization, a punch biopsy was performed. The average duration of the punch biopsy procedure was 15.6 ± 2.3 days, with a range of 11 to 21 days. In this study, the mean epidermal thickness after re-epithelialization was 197 ± 118 μ m in the control group and 208 ± 110 μ m in the I-PRF group. However, the two groups had no statistically significant difference ($p = 0.698$) (**Table 3**).

Figure 6 illustrates the histological results from H&E-stained sections: the epidermis on the I-PRF-treated side was slightly thicker than the control side.

Table 3 Epithelial thickness after re-epithelialization of the donor site

Groups	Mean $\pm$ SD (μ m)	95% CI for Mean Difference	<i>p</i> value*
Control (Bactigras)	197 $\pm$ 118		
Intervention (Bactigras + I-PRF)	208 $\pm$ 110		
Difference	-11 $\pm$ 148	[-44.7, 65.9]	0.698

*Statistical analysis was performed using a paired t-test.

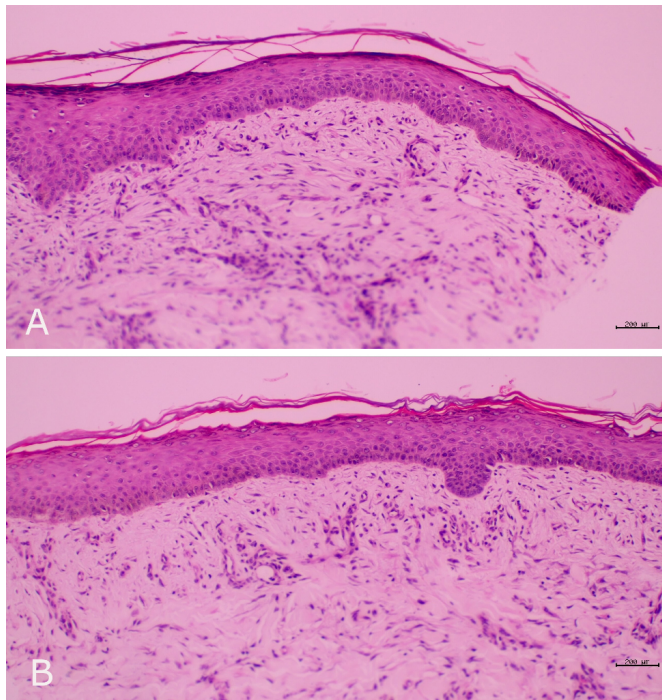


Figure 6 Specimens from the I-PRF and control sides after hematoxylin and eosin (H & E) staining showed that the epidermis was thicker on the I-PRF-treated side (A) than on the control side (B). $\times 10$

DISCUSSION

The STSG procedure is commonly used for skin and soft tissue reconstruction.¹ There are various treatment options for the STSG donor site, but the best choice has yet to be determined. Innovative wound-dressing techniques and additional procedures are being developed to enhance epithelialization and accelerate healing at donor sites.^{2,3}

I-PRF has been used to improve wound healing across various wound types.¹⁸⁻²¹ However, it remains unclear whether I-PRF can enhance epithelialization at the STSG donor site.²²⁻²⁴ This study aimed to examine the effects of I-PRF on the epithelialization of donor-site STSG wounds.

Our study found no statistically significant difference in the time required for epithelialization between the I-PRF and control groups (see **Table 2**). This result aligns with a previous study conducted by Danielsen et al.,²⁴ which also reported no statistically significant differences in the macroscopic epithelialization of donor wounds or autografts between the platelet-rich fibrin and control groups on postoperative days 5 and 8.

In contrast to previous research, Senada et al.²² Investigated the role of I-PRF in accelerating wound healing at donor sites following skin grafting in 20 burn patients. Their findings indicated that the healing time for donor sites injected with PRF was significantly shorter than that of the control sites, averaging 11.55 ± 1.39 days compared to 13.45 ± 1.70 days ($p < 0.001$). The differences between our findings and those of Senada et al. can be attributed to variations in study design and methodology. Their trial exclusively involved burn patients, whose altered physiology and systemic inflammatory responses may increase sensitivity to growth factor-based therapies such as PRF. In contrast, our study focused on a general surgical population. We standardized the donor site depth at 0.175 mm, while Senada et al. did not specify the wound depth, which could influence healing outcomes. The method of I-PRF administration may also be a critical factor. At the same time, Senada et al. utilized intradermal injections to deliver I-PRF directly into the tissue; our study employed topical application. This topical delivery might result in lower bioavailability of growth factors, as they could be partially sequestered by the primary dressing or fail to penetrate the wound bed as effectively as a direct injection. Additionally, their follow-up assessments were limited to days 10 and 14, whereas our study included more frequent evaluations starting as early as day 7 and continuing every 1 to 2 days thereafter. Such a rigorous assessment schedule may further account for the differences in observed epithelialization outcomes.

Similarly, Vaheb et al.²³ reported that the healing of donor sites was faster when treated with PRF in a study of 33 burn patients, showing significant differences on postoperative days 8 and 15 ($p < 0.001$). The differences between their findings and ours may be attributed to vari-

ations in study populations, postoperative care, and outcome assessments. Their trial specifically focused on deep burns, involved less frequent dressing changes, and had broader endpoints. In contrast, our study included a more diverse surgical cohort, utilized epithelialization-guided protocols, and measured the time to achieve more than 90% epithelialization.

Another consideration regarding our findings is the potential for local “diffusion” of various growth factors between the two adjacent study areas. In a split-body design on the same limb, bioactive molecules from the I-PRF site could diffuse through local tissue planes or systemic circulation to the control site, potentially narrowing the observable difference between groups. To ensure that no surface “contamination” occurred, we maintained a 2-cm bridge of intact skin. We used separate sterile dressings for each site, providing a physical barrier and preventing fluid communication between the proximal and distal zones.

In the histological evaluation, epithelial thickness at donor sites after re-epithelialization was assessed in both the control and I-PRF groups. Our study revealed no statistically significant difference in epithelial thickness between the I-PRF and control groups, with measurements of $208 \pm 110 \mu\text{m}$ and $197 \pm 118 \mu\text{m}$, respectively ($p = 0.698$). However, our findings differ from those of Senada et al.,²² who reported that the epidermis was significantly thicker on the PRF-treated side compared to the control side, with measurements of $195.79 \pm 26.44 \mu\text{m}$ versus $113.55 \pm 3.62 \mu\text{m}$ ($p < 0.001$). This discrepancy may be attributed to several factors, including differences in study design and the substantial variability observed in our measurements.

The high variability in epithelial thickness measurements, particularly the lack of a consistent trend between the control and intervention sides within individual patients, is a key finding of our study. This primarily reflects the inherent, substantial biological variability of the wound-healing process at the local level. While our intra-patient design optimally controls for systemic patient factors, it cannot account for micro-environmental differences within the wound. The absence of a clear directional treatment effect suggests that any potential benefit of I-PRF is minimal and likely overshadowed by this inherent biological noise. This underscores the challenge of demonstrating efficacy for interventions where the effect size is small and variable.

In our literature review and results, we observed significant variability in PRF’s impact on wound-healing outcomes. No consensus exists regarding using PRF products to treat donor site wounds after STSGs. Regarding the mechanism of action, PRF contains a higher platelet concentration than whole blood and is rich in growth factors and cytokines.^{12,13} The lack of a significant clinical difference in our study, despite these properties, suggests that further investigation into standardized preparation and delivery methods is required. Future research must explore the relationships among different PRF concentrations, preparation methods, and their effects on wound healing.

Limitations and strengths

The main limitations of our study were as follows: First, we did not quantitatively examine the concentrations of various cell populations, such as leukocytes and platelets, or specific growth factors in our I-PRF preparation. While we strictly followed the standard centrifugation protocols without modification, this remains a concern as inter-patient biological variability could still result in different concentrations of regenerative cytokines. Such variations, which were not laboratory-verified in this study, might have contributed to the lack of statistically significant differences observed. Second, we faced constraints preventing us from conducting extended patient follow-up periods.

On the positive side, our study’s strengths included using the same patient, donor site area, and STSG donor wound thickness, which allowed us to effectively compare the efficacy of I-PRF. Lastly, we conducted a histological assessment, which was crucial for measuring the mean epidermal thickness after re-epithelialization in both groups.

CONCLUSION

This prospective, randomized, controlled intra-patient study found that the use of I-PRF did not significantly improve epithelialization rates or increase epithelial thickness in STSG donor sites compared to standard care. Consequently, the routine use of I-PRF for this specific purpose is not recommended. By omitting this unnecessary procedure, the surgical process can be streamlined, operative time reduced, and significant cost savings achieved, all without compromising patient outcomes. However, we acknowledge that further research is needed to fully assess its potential benefits in various clinical scenarios.

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